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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/261,329
Filing Date: March 03, 1999
Appellant(s): ANDERSEN ET AL.

Elias J. Lambiris
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 2, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 204, 206 and claim 205 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 204 and 206 stand finally rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 204 is directed to a genus of modified cellulases comprising a substitution of the amino acid at position 119 with H in the amino acid sequences of SEQ ID NO: 5 (numbering according to SEQ ID NO:1) and having endoglucanase activity. Because "comprising " is open language, the claim allows for an undefined number of substitutions in addition to Q119H and reads on any structure that is not necessarily homologous with SEQ ID NO:5. Claim 206 is drawn to the modified cellulase of claim 204 further comprising a substitution at the specific position with the specific amino acids.

Thus, claims 204 and 206 are directed to a genus of cellulases exhibiting endoglucanase activity and having undefined structures. The specification teaches the structure of only a single representative species of said genus, the modified endoglucanase from *Thielavia terrestris* having the sequence of SEQ ID NO: 5 with the single substitution Q118H corresponding to the substitution Q119H in SEQ ID NO:1. The rest of the amino acid sequence of said modified cellulase, 200 amino acids, is

identical to SEQ ID NO:5 (201 amino acids). However, the genus of modified endoglucanases comprises variants additionally mutated at any of said 200 amino acid residues. Therefore, many functionally and structurally unrelated endoglucanases are encompassed within the scope of these claims, including partial amino acid sequences. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a modified cellulase having endoglucanase activity. This is insufficient to put one of skill in the art in possession of the entire claimed genus. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 204 and 206 stand finally rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified cellulase having endoglucanase activity and the amino acid sequence of SEQ ID NO: 5 with a single substitution corresponding to a substitution Q119H in SEQ ID NO:1 (Q119H substitution), does not reasonably provide enablement for a modified cellulase having endoglucanase activity and an amino acid sequence comprising substitution Q119H and having an undefined percent identity to SEQ ID NO: 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 204 and 206 are directed to a modified cellulase having endoglucanase activity and comprising substitution Q119H and additional substitutions. Because "comprising " is open language the claims read on any endoglucanase structure with an undefined percent homology to SEQ ID NO: 5. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The state of the art does not allow the predictability of the properties based on the structure. The specification does not teach which residues besides the specifically substituted are responsible for the resulting properties of the modified cellulase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of modified cellulases having endoglucanase activity broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired properties/activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of substitution and which are

conserved (i.e. expectedly intolerant to substitution), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and amino acid sequence of a single modified cellulase with substitution Q119H in SEQ ID NO:5.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid substitutions can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such substitutions is unpredictable. In addition, one skilled in the art would expect any tolerance to substitution for a given protein to diminish with each further and additional substitution, e.g. multiple substitutions.

The specification does not teach a rational and predictable scheme for substituting any residues in SEQ ID NO:5 with an expectation of obtaining the endoglucanase function that is exhibited by a disclosed mutant and the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Therefore, one skilled in the art would require guidance beyond that provided in the specification as to how to make a modified cellulase having endoglucanase activity with the amino acid sequence of an unknown homology to SEQ ID NO:5. Without such guidance, the experimentation left to those skilled in the art is undue.

Claims 204-206 stand finally rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 204-206 are drawn to a modified cellulase comprising a substituion Q119H "in the amino acid SEQ ID NO:5, wherein each position is numbered according to the amino acid sequence of the cellulase of SEQ ID NO:1". It is confusing to define a position number in one specific sequence (SEQ ID NO:5) using another sequence (SEQ ID NO:1) as opposed to the direct numbering the position in SEQ ID NO:5. It is unclear what limitaion is imposed on the scope of the claims by using said indirect numbering via SEQ ID NO:1. The specification discloses the alignment of SEQ ID NOs: 1 and 5 (pages 7-12, Table 1, columns 1 and 5, respectively). SEQ ID NO:1 has 202 amino acids whereas SEQ ID NO:5 has 201 amino acids. As shown in Table 1, SEQ ID NO:5 does not have an amino acid at the position corresponding to position 49 of SEQ ID NO:1. Thus, position Q118 in SEQ ID NO:5 corresponds to position Q119 in SEQ ID NO:1.

Claim 206 is furhter confusing as reciting positions 21a, 49a, 49b, 95j and 150b. Neither SEQ ID NO:1 nor SEQ ID NO:5 has these positions (Table 1).

(11) Response to Argument

Appellants first provide "the legal standard" for their arguments regarding the 112, 1st paragraph written description rejection. They state that "The written description requirement can be met by showing that an invention is complete by disclosure of

sufficiently detailed, relevant identifying characteristics, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics. See, e.g., University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997)., Enzo Biochem v. Gen-Probe Inc., 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). A description of a claimed genus may be achieved by recitation of a representative number of species falling within the scope of the genus or by a recitation of structural features common to the members of the genus which constitute a substantial portion of the genus. See University of California B. Eli Lilly and Co., 43 U.S.P.Q.2d at 1569" (Appeal Brief, page 4, 1st paragraph). Appellants further reinstate "These [The Patent Office] guidelines reiterate the Federal Circuit's law that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by relevant identifying characteristics, i.e., structure or other physical and/or chemical characteristics, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In particular, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such

characteristics." Guidelines for Examination of Patent Applications under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement. 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001). The Written Description Guidelines also state that a representative number of species requires that the species which are expressly described be representative of the entire genus. The Written Description Guidelines further state that what constitutes a representative number is an inverse function of the predictability of the art" (page 4, 2nd paragraph). Appellants argue that "The claimed invention is drawn to modified cellulases of SEQ ID NO: 5, comprising a substitution of the amino acid at position 119 with H, wherein the variant has endoglucanase activity. Thus, the claims require that (1) the parent cellulase is the cellulase of SEQ ID NO: 5, (2) the modified cellulase comprises a specific substitution at a specific position, and (3) the modified cellulase has endoglucanase activity. Because of these claim requirements, the claims provide structural limitations on the modified cellulases of the present invention" (paragraph bridging pages 4-5).

This is not persuasive because Appellants disclose neither structure, other physical and/or chemical characteristics nor functional characteristics coupled with a known or disclosed correlation between function and structure. As discussed above, there is no limitation on the structure except that it contains a single substitution. With regard to the properties, it can be an endoglucanase activity combined with any properties such as thermostability, detergent stability, etc. Therefore, while the parent cellulase is defined as the cellulase of SEQ ID NO: 5, the claimed modified cellulase has an undefined homology to SEQ ID NO:5. While it is agreed that "what constitutes a

representative number is an inverse function of the predictability of the art", in the instant case the number of claimed structures is indefinite and the representative number is one. The claimed structures are defined by a single amino acid only. While it is possible to attempt to predict the result of a substitution in a highly homologous structure, the predictability is impossible when the structure cannot be modeled using the parent cellulase, i.e. when the parent and the claimed endoglucanases have low or no homology. Appellants argue that "Moreover, the specification specifically describes a number of other positions and mutations, which can be combined with the claimed substitution. For example, the variants may further comprise any of the substitutions recited in claim 206. Moreover, the specification describes at pages 22-24 the introduction of disulfide bridges and mutations in the substrate binding cleft to stabilize the parent cellulase. Examples of such mutations are provided in Tables 4-6 at pages 28-35 of the specification" (page 1, 1st full paragraph). This is not agreed with because the specification discloses only a single species comprising substitution Q119H, said species having no other additional substitutions. With regard to claim 206, the claimed structure is not limited to a substitution Q119H and a second substitution. Appellants further argue "Thus, the Examiner is incorrect that the specification fails to describe any other species. Contrary to the Examiner's allegations, the specification discloses numerous modified cellulases of the present invention and evidences that Applicants possessed these species. These species are a representative number of species within the scope of the genus and therefore Applicants' disclosure evidences that Applicants were in possession of the claimed genus of modified cellulases at the time the

application was filed" (page 5, 2nd full paragraph). This is not agreed with because while the specification teaches various positions of potential interest, these positions are not claimed and, most importantly, the claimed endoglucanase structure is not limited to any specific substitutions except a single substitution Q119H (claim 204) or Q119H and a second specific substitution (claim 206). While it is possible to attempt to predict the effect of a second substitution based on the guidance provided by the specification, it is impossible to predict the effect of multiple additional substitutions that are allowed by the claims.

Appellants further argue "Moreover, the level of skill in the ad of enzyme variants is very high. Indeed, there are numerous U.S. patents on cellulase variants comprising a mutation at one or more positions. Examples of recently-issued U.S. patents are U.S. Patent Nos. 5,792,641, 6,1 14,296, 6,1 17,664, 6,187,732, and 6,268,328. It would be routine for one of ordinary skill in the art to combine the substitution recited in claim 204 of the present application with any of the mutations described in the prior ad. Applicants note that the claims of g.!! of these patents use the transition term "comprising". Copies of U.S. Patent No. 6,268,328 as well as two other U.S. patents (U.S. Patent Nos. 6,117,664 and 6,682,924), which claim enzyme variants comprising one or more mutations, are enclosed herewith" (page 5, 3rd full paragraph). This is not persuasive because each issued patent has its own set of disclosure, art, examining considerations and prosecution history. It would require the familiarity with all of that to provide a comment which in itself is inappropriate for the examiner to make.

With regard to the 112, 1st paragraph enablement rejection, Appellants first provide "the legal standard" asserting "The question, then, is whether in an unpredictable art, section 1 12 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with 'thousands' of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid 'literal' infringement of such claims by merely finding another analogous catalyst complex which could be used in 'forming hydroperoxides.' " (page 8, 2nd full paragraph). It is noted that that the similarity between the situation discussed above and the instant case is not clear. It appears as contradictory that Appellants discuss "an unpredictable art" to support the issues in what they consider "a predictable art". Unlike, in the discussed case, in which one out of forty examples did not work (page 8, 1st full paragraph), the instant application discloses only one example while claiming an indefinite number of modified cellulases. Appellants further argue that "while some experimentation might be necessary, as long as the experimentation was not "undue experimentation," the claims would not violate 35 U.S.C. 112, Angstadt, Id" (page 9). This is not persuasive because making variants within the full scope of the current claims would still require undue experimentation in

view of the following considerations. While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants useful as endoglucanases requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. Claims 204 and 206 include many variants with more than minor but with substantial modifications to the structure of the parent enzyme, where each additional modification renders its effect less predictable. As such the amount of experimentation required to make the currently claimed scope is still deemed to be undue.

With regard to the 112, 2nd paragraph rejection, Appellants first provide "the legal standard" asserting that "The test for determining whether a claim complies with the definiteness requirement is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." Morton International, Inc. F. Cardinal Chemical Co., 28 U.S.P.Q.2d 1190, 1994 (Fed. Cir. 1993)" (page 11). Appellants also state that "It is also well settled that a patentee may act as his own

lexicographer and expressly define terms in the specification. See, e.g., *Housey Pharmaceuticals Inc. v. Astra Zeneca UK Ltd.*, 70 U.S.P.Q. 1641, 1644 (Fed. Cir. 2004)" (page 11). Appellants then argue that "Based on Applicants' disclosure, one of ordinary skill in the art would know how to align the amino acid sequence of another cellulase and the cellulase of SEQ ID NO: 1 and then be able to determine the positions in other cellulases corresponding to the positions of the cellulase of SEQ ID NO: 1. Therefore, the claims, read in the light of the specification, reasonably apprise those skilled in the art of the scope of the invention and provide clear warning to persons in the art of what will constitute infringement. Moreover, an applicant has the right to be his own lexicographer. Thus, an Examiner cannot require an applicant to use claim language which she prefers, e.g., to recite the positions according to the amino acid sequence of SEQ ID NO: 1, as long as the claims satisfy the definiteness requirement.

Further evidence that the claim language is clear and definite is the following statement at page 10 of the Office Action mailed October 3, 2003:

> Claim 203 rewritten to be drawn to a mutant with a single mutation Q1 18H in SEQ ID NO: 5 would be allowable. Q118H in SEQ ID NO: 5 corresponds to Q119H in SEQ ID NO: 1" (page 12).

This is not persuasive because there is no issue of a special meaning assigned to a term but rather an issue with the fact that it is unclear what limitations are imposed by bringing into the claim any reference to SEQ ID NO:1 when a single sequence of SEQ ID NO: 5 is the parent sequence. Furthermore, the fact that after the examination of the application the examiner understands what Appellants intend to claim does not render the claim clear.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

E. Slobodyansky

Elizabeth Slobodyansky, PhD
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Art Unit 1652

October 13, 2004

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